PATENT SPECIFICATION

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COMPLETE SPECIFICATION

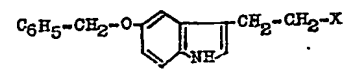
Improvements in or relating to the Preparation of 5-Hydroxy-Tryptamine and Intermediates therefor

We, ROMEO JUSTONI, an Italian citizen, of Viale Regina Giovanna 39, Milan, Italy, and FRANCESCO VISMARA S.p.A., a Body Corporate organised under Italian law, of Casatenovo, Brianza, Como, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with improvements in or relating to the preparation of the therapeutically active compound 5-hydroxy-tryptamine.

Various expensive procedures for the synthesis of 5-hydroxy-tryptamine have already been proposed; we have now discovered a new process for the preparation of this compound employing certain novel intermediates which are illustrated below, which is more advantageous than the processes proposed hereto.

The intermediates used in our new process are indole derivatives which may be represented by the following general formula



I

where X is —COOH or —COOR (R being a straight or branched alkyl group containing up to 5 carbon atoms), —CO—NH—NH_2, —CON_3, —N=CO, —NH—COOR (R having the above-stated meaning) or —NH—$COOCH_2$—C_6H_5.

The invention comprises, as a new compound, the compound of formula I in which X is —CON_3, namely 5-benzoyloxy-indole-3-β-propionazide

The starting material for the synthesis of 5-hydroxy-tryptamine is 5-benzyloxy-indole-2-carboxy-3-β-propionic acid, which may be prepared according to the directions given in our copending application No. 9600/55 (Serial No. 766,036).

According to the present invention, this indole dicarboxylic acid is first converted into a benzyloxy-indole monocarboxylic acid (Formula I above where X=COOH) which, besides the 5-benzyloxy group, only contains in the indole nucleus a CH_2—CH_2—COOH side chain in the 3-position. This compound is then submitted to a number of transformations, through a series of intermediates, in order to convert the carboxylic-3-side-chain into a —CH_2—CH_2—NH_2 side-chain, and to convert the 5-benzyloxy group into a free 5-hydroxyl group.

In practising our invention we proceed as follows: 5-benzyloxy-indole-2-carboxyl-3-β-propionic acid is heated at 190—230° C. alone or in solution and/or suspension in an inert high-boiling liquid, suitable high-boiling liquids being Tetralin (Registered Trade Mark), decalin and neutral petroleum derivatives having a boiling point above 100° C., such as paraffin oil; mono-decarboxylation of the dicarboxylic acid occurs and 5-benzyloxy-indole-3-β-propionic acid (Formula I where: X=COOH; M.Pt. 163—165° C., from dilute ethanol) is obtained.

This indole mono-carboxylic acid is esterified with a low molecular alcohol in order to obtain a corresponding ester: for example the methyl-ester (formula I where: X=$COOCH_3$ M.Pt. 98—101° C., from methanol), the ethyl ester (formula I where: X=$COOC_2H_5$, M.Pt. 62—63° C., from hexane) and other similar esters with alkyl groups containing up to 5 carbon atoms.

By boiling with an alcoholic hydrazine hydrate solution the so-obtained ester is then converted into the corresponding hydrazide (formula I where: X=CO—NH—NH_2;

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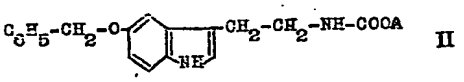
M.Pt. 137—138° C., from dilute ethanol).

By treating the said hydrazide with sodium nitrite and an acid in presence of water and of a solvent selected from ether, benzene and its methyl homologues and aliphatic alcohols containing 4 or 5 carbon atoms, the novel azide (formula I where: $X = CON_3$) is readily obtained.

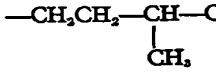
As we have verified this azide—by pyrolysis at 60—140° C., in an inert solvent, and subsequent mild hydrolysis of the so formed isocyanate (formula I where: $X = NCO$) with an aqueous mineral acid—may be directly transformed into 5 - benzyloxy - tryptamine which, in its turn, may be converted into 5-hydroxy-tryptamine. However we point out that this way of transforming the above azide into 5-hydroxy-tryptamine furnishes only a very poor yield.

On the contrary we have discovered that it is possible in the practice of our invention to convert the said azide into 5-hydroxy-tryptamine by a better indirect procedure through certain further intermediate compounds. The transformation is carried out as follows. The azide is heated at 60—140° C. with methyl alcohol, ethyl alcohol, another low molecular alcohol containing up to 5 carbon atoms or benzyl alcohol. Pyrolysis occurs and the transitorily formed isocyanate, by reaction with the alcohol employed, yields an urethane (formula I where X is: NH—$COOCH_3$, NH—$COOC_2H_5$, NH—$COOC_3H_7$ (normal and iso), NH—$COOC_4H_9$ (normal and isomers), NH—$COOC_5H_{11}$ (normal and isomers), or NH—$COOCH_2$—C_6H_5). The constitution of these urethanes is also clearly illustrated by the following general formula:—



II

where: A = alkyl or aralkyl group according to the alcohol employed in its preparation. For example, employing methanol the methyl-urethane—i.e. β-[3-(5-benzyloxy)-indolyl]-ethyl-carbamic acid methyl ester—(Formula II where: A = —CH_3; M.Pt. 94—95° C.—from benzene by mixing with a small quantity of hexane—) is obtained. Similarly: ethanol yields the ethyl urethane (Formula II where: A = —C_2H_5; M.Pt. 87—88° C.—from benzene with hexane—); isoamyl alcohol yields the corresponding isoamylurethane (Formula II where: A =



non-crystalline pale yellow glass); benzyl alcohol yields the benzyl urethane (Formula II where: A = —CH_2—C_6H_5: M.Pt. 72—73° C.—from benzene with hexane—).

The urethane is then subjected to a mild catalytic hydrogenolysis in the presence of a palladium catalyst in an alcohol solution; by removal of the benzyl group from the 5-benzyloxy function, the corresponding non-benzylated urethane having a free 5-hydroxyl group is formed; hydrolysis of the latter, in an alcohol solution, employing as hydrolysing agent a mineral acid in the presence of water, gives, by splitting off the carbamic ester group, the desired 5-hydroxy-tryptamine which is isolated in the form of its picrate, or of its double salt with creatinine (sulphate).

Particularly when the benzyl-urethane derivative (Formula II where

$$A = —CH_2—C_6H_5,$$

or formula I where:

$$X = NH—COOCH_2C_6H_5)$$

is prepared as intermediate, the catalytic hydrogenolysis thereof in the presence of an aqueous alcohol and a mineral acid, furnishes directly a very high yield of 5-hydroxy-tryptamine.

Again we have found that the conversion of any intermediate benzyloxyurethane (Formula II) into 5-hydroxy-tryptamine may be obtained by carrying out the same reactions—hydrogenolysis and hydrolysis—in an inverted order, i.e. firstly hydrolysis and then hydrogenolysis. In this case hydrolysis of the urethane in the presence of a mineral acid yields 5-benzyloxy-tryptamine which is isolated in the form of its salicylate or benzoate.

Catalytic hydrogenolysis thereof in an alcohol solution gives a solution containing the corresponding salts of 5-hydroxy-tryptamine, from which the indole base may be isolated in the form of its picrate.

In order that the invention may be well understood the following examples are given by way of illustration only:—

EXAMPLE I.

Ten 20 g portions of 5-benzyloxy-indole-2-carboxyl - 3 - β-propionic acid (prepared according to the directions of our copending Application No. 9600/55 (Serial No. 766,036)) were heated at 215—225° in an oil bath; melting and decarboxylation occurred. The heating was continued for one hour. After cooling, all the obtained brownish solids were taken up with warm 70% aqueous ethanol and the solution filtered with charcoal. Dilution with water to bring the alcohol to 50% and cooling caused the separation of 153 g of crude 5-benzyloxy-indole-3-β-propionic acid melting at 150—151° C. with sintering at 118° C. This product recrystallised from the minimal amount of 50%

aqueous ethanol melts at 153—156° C.: yield 105.5 g (61% of the theoretical amount). (An analytical sample twice recrystallised from 50% ethanol melts at 163—165° and the nitrogen determination is in good agreement with formula $C_{18}H_{17}O_3N$: N% Calc. 4.74, N% Found 4.79.)

A solution of 100 g of the above crude 5-benzyloxy-indole-3-β-propionic acid in 1000 cc of absolute methanol containing 3% of dry hydrogen chloride was refluxed for a period of two hours. After cooling, the mixture was poured into a solution of 103 g of sodium bicarbonate in 2150 cc of water. The separated crystalline brownish solid was collected on a filter and washed with water giving 103 g of methyl-5-benzyloxy-indole-3-β-propionate: M.Pt. 98—99° C. (An analytical sample recrystallised from methanol shows M.Pt. 100—101° C.; for $C_{19}H_{19}O_3N$: N% Calc. 4.53, N% Found 4.37).

A mixture of 100 g of the above methyl-5-benzyloxy-indole-3-β-propionate, 2700 cc of ethanol and 145 cc of hydrazine hydrate was heated under reflux for one hour. After removal under reduced pressure of most of the solvent, the residual solution was diluted with an equal volume of water, and the precipitated crystalline solid was filtered and washed with water. The M.Pt. of the crude hydrazide was 133—135° C. After crystallisation from 70% ethanol, pure 5-benzyloxy-indole-3-β-propion-hydrazide was obtained in an amount of 95 g (96% of the theoretical amount): M.Pt. 134—136° C. (An analytical sample, recrystallised from water, melts at 137—138° C.: for $C_{18}H_{19}O_2N_3$ N% Calc. 13.59, N% Found 13.70).

To a solution of 90 g of the crude above hydrazide in 270 cc of acetic acid, 1140 cc of water chilled to 0° C. and 750 cc of benzene were added with stirring. The resulting mixture was then treated with 225 cc of a 10% aqueous sodium nitrite solution, stirring being continued for five minutes more. After separating the benzene layer, the aqueous phase was extracted twice with 750 cc portions of benzene. The cooled combined benzene extracts to 0° C., washed firstly with a cooled dilute sodium bicarbonate aqueous solution and then with cooled water until neutral, were dried over finely powdered anhydrous sodium sulfate. (A sample (15 cc) of the filtered benzene solution, evaporated to dryness under reduced pressure at room temperature, gave a yellow crystalline residue of crude 5-benzyloxy-indole - 3-β-propionazide which began to decompose at 45° C.).

The above benzene solution was added dropwise to 7500 cc of boiling anhydrous methanol. Continuous distillation of the azeotropic mixture of methanol and benzene occurred.

When all the benzene had been added and distilled, the residual methanol solution was refluxed for one hour and then evaporated under reduced pressure to dryness thus obtaining a brownish oil. A concentrated benzene solution of this oil was poured over 150 g of aluminium oxide and the formed β-[3-(5-benzyloxy) - indolyl]-ethyl carbamic acid methyl ester was completely eluted by washing the aluminium oxide with benzene. Evaporation of benzene solution at reduced pressure to a small volume (about 300 cc) and dilution with 30 cc of hexane gives 60.9 g of the methylurethane as white needles M.Pt. 90—93° C. The mother liquors were again treated with aluminium oxide so obtaining a further amount of the same product. Total yield 70.5 g. (An analytical sample twice recrystallised from benzene-hexane melts at 94—95° C.: the nitrogen content is in good agreement with the formula $C_{19}H_{20}O_3N_2$: N% Calc. 8.64, N% Found 8.72).

A solution of 20 g of the above methylurethane in 700 cc of methanol was treated with hydrogen with continuous stirring at five atm. pressure (room temperature: about 25° C.) in presence of 10 g of a 10% palladium on carbon catalyst until no more hydrogen was adsorbed (about five hours). The filtered methanolic solution contains β - [3 - (5-hydroxy)-indolyl]-ethyl carbamic acid methyl ester. It was then evaporated under reduced pressure to a volume of about 300 cc.

(That the debenzylation was accomplished was proved by the fact that a sample of this solution treated in an alkaline medium with an aqueous solution of diazotised sulphanilic acid gave a red colour so confirming the presence of a substance having a free phenolic group).

The crude methanolic solution containing the β-[3-(5-hydroxy)-indolyl]-ethyl carbamic acid methyl-ester was refluxed with 100 cc of dilute hydrochloric acid (1:1) for 30 minutes to hydrolyse the carbamic ester. The greenish solution, after addition of 6 g of crystallised sodium acetate, was neutralised to Congo red with sodium bicarbonate and filtered from the separated sodium chloride. 13.5 g of picric acid were added to the filtrate, and most of the alcohol was evaporated under reduced pressure. The residual orange-red mixture was diluted to about 300 cc with water, warmed to 50—65° C. and filtered with charcoal: by cooling 5-hydroxy-tryptamine picrate separated off as red needles M.Pt. 185—187° C. with dec.; after concentration of the mother liquors under reduced pressure a further amount of the same picrate was obtained. (A sample recrystallised from water melts at 196—197° C. and a mixed melting point with an authentic sample gives no depression).

EXAMPLE 2.

A portion of β-[3-(5-benzyloxy)-indolyl]-ethyl carbamic acid methyl ester prepared in Example 1 was treated by a somewhat dif-

ferent procedure: the later steps for transforming this intermediate into 5-hydroxy-tryptamine were inverted as follows: firstly hydrolysis was carried out by treating a solution of 20 g of the methyl-urethane in 280 cc of ethanol with 120 cc of 6 N hydrochloric acid overnight at 40—50° C.: hydrolysis of the carbamic ester group occurred. To the so obtained solution containing 5-benzyloxy-tryptamine hydrochloride, 53 g of sodium bicarbonate were added to neutralise the excess of hydrochloric acid. After filtration of the separated sodium chloride, 10 g of sodium salicylate were added with stirring and the ethanol was evaporated under reduced pressure up to a residual volume of about 140 cc. By cooling crystallisation occurred; the collected 5-benzyloxy-tryptamine salicylate, washed with a little water and dried, forms yellow crystalline needles melting at 167—169° C. (A water recrystallised analytical sample in form of white needles shows M.Pt. 174—175° C.: the nitrogen determination is in good agreement with the formula $C_{17}H_{18}ON_2.C_7H_6O_3$ or $C_{24}H_{24}O_4N_2$: N% Calc. 6.92, Found 7.01).

A solution of 10 g of the above 5-benzyloxy-tryptamine salicylate in 300 cc of ethanol was treated with hydrogen at five atm. pressure with continuous stirring (room temperature: about 25° C.) in presence of 5 g of 10% palladium on carbon catalyst until no more hydrogen was adsorbed. From the filtered alcoholic solution containing 5-hydroxy-tryptamine salicylate, the indole base was separated as the picrate by adding 5.7 g picric acid as already was described at the end of Example 1. By evaporating the orange-red solution to a small volume crystallisation begins. The filtered 5-hydroxy-tryptamine picrate was washed with ether to eliminate any trace of salicylic acid and recrystallised from water; it is so obtained in form of red needles melting at 196—197° also when mixed with an authentic sample.

EXAMPLE 3.

A 20 g portion of the β-[3-(5-benzyloxy)-indolyl]-ethyl-carbamic acid methyl ester, prepared in Example 1, was hydrolysed in a perfectly analogous way as in Example 2. To the neutralised aqueous ethanolic solution filtered from sodium chloride, 9 g of sodium benzoate were added. By concentration under reduced pressure, 5-benzyloxy - tryptamine benzoate as yellow needles, M.Pt. 148—149° C. was obtained. (An analytical sample twice recrystallised from water melts at 153—154° C. and the nitrogen content determination is in good agreement with the formula $C_{17}H_{18}ON_2.C_7H_6O_2$ or $C_{24}H_{24}O_3N_2$: N% Calc. 7.22, N% Found 7.40).

Analogously as in Example 2 an alcoholic solution of 5-benzyloxy-tryptamine benzoate was treated with hydrogen in presence of 10% palladium on carbon catalyst. By addition of picric acid (5.7 g) and concentration of the orange-red solution, the 5-hydroxy-tryptamine picrate was separated by handling as described at the end of Example 2.

EXAMPLE 4.

70 g of 5-benzyloxy-indole-2-carboxyl-3-β-propionic acid (prepared according to the directions of our copending application No. 9600/55 (Serial No. 766,036)) were finely suspended in 700 cc of paraffin oil (B.Pt. >330° C.) and heated to 210—220° C. with continuous stirring at reduced pressure (about 300 mm) until no more carbon dioxide evolved. After cooling the mixture was extracted with a concentrated aqueous sodium carbonate solution: the pH of the obtained brown solution was then adjusted to about 7.2 (±0.1) and the solution was filtered with charcoal from separated tar. By acidification with dilute hydrochloric acid, 38.8 g of the crude 5-benzyloxy-indole-3-β-propionic acid separates off. After crystallisation from aqueous ethanol the product melts at 161—163° C.

A solution of 34 g of the above crude indole-monocarboxylic acid in 340 cc of absolute ethanol containing 3% of dry hydrogen chloride was refluxed for two hours. After cooling the mixture was poured into a solution of 35 g of sodium bicarbonate in 700 cc of water thus obtaining 35 g of the crude ethyl 5-benzyloxy-indole - 3 - β - propionate which after crystallisation from hexane melted at 62—63° C. and is in good agreement with the formula $C_{20}H_{21}O_3N$: N% Calc. 4.33, N% Found 4.48.

A mixture of 33.5 g of the above ethyl ester, 900 cc of ethanol and 48 cc of hydrazine hydrate was refluxed for one hour. By treating the solution in the same way as described in Example 1 for the transformation of the corresponding methyl ester into the hydrazide, 31 g of crude 5-benzyloxy-indole - 3-β-propionhydrazide, M.Pt. 133—134° C. were obtained. (The mixed melting point with a pure sample gives no depression).

30 g of this hydrazide were converted into the azide using acetic acid and sodium nitrite according to the directions of Example 1 with the sole difference that ether was employed in place of benzene. The so obtained dried ethereal solution (about 500 cc), containing the 5-benzyloxy-indole - 3-β-propionazide, was added dropwise to 1000 cc of boiling anhydrous ethanol in such a rate that the ether distills off. When all the ethereal solution had been added and distilled, the residual ethanolic solution was refluxed for one hour and then evaporated to dryness under reduced pressure thus obtaining a brownish oil. A concentrated benzene solution of this oil was poured over 50 g of aluminium oxide and the β-[3-(5-benzyloxy)-indolyl]-ethyl carbamic acid ethyl ester was

completely eluted by washing the aluminium oxide with benzene.

Evaporation of benzene solution to a small volume (about 100 cc) and dilution with 10 cc of hexane gives about 21 g of the said ethyl urethane. The mother liquors were again treated with aluminium oxide so obtaining a further amount of the same product. Total yield 24.2 g: M.Pt. 86—87° C. (An analytical sample twice recrystallised from benzene hexane melts at 87—88° C. The nitrogen determination is according to the formula $C_{20}H_{22}O_3N_2$: N% Calc. 8.28, N% Found 8.05).

A solution of 20 g of the above ethyl-urethane in 700 cc of ethanol was treated with hydrogen with continuous stirring at five atm. pressure (room temperature: about 25° C.) in the presence of 10% palladium carbon catalyst until no more hydrogen was adsorbed (about five hours). The filtered solution which contained β-[3-(5-hydroxy)-indolyl]-ethyl carbamic acid ethyl ester, was then evaporated under a reduced pressure to a volume of about 300 cc.

The crude solution of the non-benzylated ethyl urethane was refluxed with 100 cc of dilute hydrochloric acid (1:1) for 30 minutes to hydrolyse the carbamic ester group. The green solution, after addition of 6 g of crystallised sodium acetate, was neutralised to Congo red with sodium bicarbonate and filtered from the separated sodium chloride. 13.5 g of picric acid were added to the filtrate, and most of the alcohol was evaporated under reduced pressure. The residual orange-red mixture was diluted to about 300 cc with water, warmed to 60—65° C. and filtered with charcoal; by cooling 5-hydroxy-tryptamine picrate separated off as red needles M.Pt. 185—187° C. with dec.; after concentration of the mother liquors under reduced pressure a further amount of the same picrate was obtained.

Example 5.

375 g of 5 benzyloxy-indole-2-carboxyl-3-β-propionic acid (prepared according to the directions of our copending Application No. 9600/55 (Serial No. 766,036)) were refluxed with 3000 cc of boiling Tetralin (Registered Trade Mark) for seven hours, until the evolution of carbon dioxide had ceased. After cooling, the separated crystalline product was filtered and dried: 276 g of 5-benzyloxy-indole-3-β-propionic acid, melting at 153—157° C. were obtained. Concentration of the mother liquors under reduced pressure gives a second crop of 25.8 g melting at 151—155° C. The total yield of 5-benzyloxy-indole-3-β-propionic acid amounted in this way to about 92% of the theoretical amount; the product was satisfactory for the next step. (A mixed melting point of a sample recrystallised from aqueous ethanol with a pure sample of the indole monocarboxylic acid gives no depression). By extraction of the residual mother liquor with a dilute aqueous sodium bicarbonate solution and following acidification thereof, 23 g of a mixture of mono- and not changed bi-carboxylic acid melting at 171—176° C. were obtained. This third crop may be recycled so giving a further small amount of 5-benzyloxy-indole - 3-β-propionic acid.

The same procedure has been experienced using decalin as solvent for the decarboxylation: a similarly good yield of the same indole-monocarboxylic acid was obtained.

295 g of this indole monocarboxylic acid were converted, via the methyl ester (yield 292 g), into hydrazide (yield 280 g) and then into azide according to the directions of Example 1.

The so obtained dried benzene solution of 5-benzyloxy-indole - 3 - β-propionazide was added dropwise to 350 cc of anhydrous benzyl alcohol warmed at 130° C. in an oil bath: continuous distillation of benzene occurred. The solution was warmed at 130° C. for 30 minutes more after complete distillation of benzene. 350 cc of xylene were added and the resulting brown solution was evaporated to dryness under reduced pressure. The residual oil was dissolved in 350 cc of benzene and poured onto a column of 700 g of aluminium oxide.

After complete elution with benzene the eluted solution was concentrated under reduced pressure to about 350 cc: addition of 60—70 cc of hexane causes the crystallisation of 234 g of β-[3-(5-benzyloxy)-indolyl]-ethyl carbamic acid benzyl ester, as white needles melting at 70—72° C. The mother liquors were again treated with aluminium oxide so obtaining a further crop of the same product. Total yield 276 g (77% of the theoretical amount). (An analytical sample recrystallised from benzene-hexane melts at 72—73° C. and the determination of nitrogen content is in good agreement with the formula $C_{25}H_{24}O_3N_2$: N% Calc. 7, N% Found 6.81).

To a solution of 270 g of the above benzyl-urethane in 27 l. of ethanol and 675 cc of normal hydrochloric acid, 135 g of 10% palladium on carbon catalyst were added. The mixture was treated with hydrogen with continuous stirring at six atm. pressure (room temperature: about 25° C.) until no more hydrogen was adsorbed (about 80 hours). To the so-obtained ethanolic solution, filtered from the catalyst, containing the 5-hydroxy-tryptamine hydrochloride, 162 g of picric acid were added. Elimination of the ethanol under reduced pressure to a volume of 4 l. caused the crystallisation of most of the 5-hydroxy-tryptamine picrate as red needles: 205 g M.Pt. 185—186°. By concentration of the mother liquors further crops of crystals were collected: the total yield amounted to

270 g (about 85%). (A mixed melting point of a water recrystallised sample with pure 5-hydroxy-tryptamine picrate gives no depression).

We point out that 5-hydroxy-tryptamine may be separated from the alcoholic solution, after the palladium-hydrogen treatment, in the form of its well known double salt with creatinine (sulphate). The handling is as follows: to a ethanolic solution—obtained by treatment of 27 g of benzylurethane with hydrogen in presence of 10% palladium on carbon catalyst according to the above directions—7.65 g of creatinine and then 67.5 cc of 2 N sulphuric acid were added. The mixture was heated to boiling with stirring and then cooled to 0° C. 5-hydroxy-tryptamine-creatinine-sulphate separated off as white crystalline precipitate. The product was filtered on a Büchner funnel, washed with ethanol and dried: yield 25 g: M.Pt. 210—211° C. with dec. (A water recrystallised sample melts at 213—214° C. with dec. and does not give depression when mixed with an authentic sample of 5-hydroxy-tryptamine-creatinine-sulphate).

We have again experienced that, after the benzene solution of the 5-benzyloxy-indole-3-β-propionazide (from 280 g of hydrazide) has been reacted with benzyl alcohol and all the benzene distilled, the crude benzyl alcohol solution of the β-[3-(5-benzyloxy)-indolyl]-ethyl-carbamic acid benzyl ester, when diluted to 27 l. with ethanol containing 700 cc of N hydrochloric acid, may be directly submitted to palladium-hydrogen treatment in a perfectly analogous way. In this case all the benzyl alcohol present was transformed into toluene. After elimination of the catalyst from the hydrogenated solution 5-hydroxy-tryptamine picrate, as well as 5-hydroxy-tryptamine-creatinine-sulphate, was obtained in a similar high yield.

EXAMPLE 6.

A solution of 50 g of 5-benzyloxy-indole-3-β-propionic acid (obtained according to the directions given in first part of Example 5) in 500 cc of isoamyl alcohol containing 3% of dry hydrogen chloride was refluxed over a period of two hours. After cooling, the mixture was first washed with an excess of a dilute aqueous sodium bicarbonate solution and then with water until neutral thus obtaining an isoamyl alcohol solution of isoamyl-5-benzyloxy-indole-3-β-propionate.

(To recognise the presence of this ester, a sample—35 cc—of this solution was dried over magnesium sulphate and then evaporated to dryness in vacuo. A concentrated benzene solution of the residual brownish oil was chromatographed on 50 g of aluminium oxide. After complete elution with hexane, benzene and a mixture consisting of equal volumes of benzene and ether, followed by evaporation of eluates under reduced pressure, the isoamyl ester was obtained as a pale yellow glass: 3.2 g. The latter was dissolved in 70 cc of ethanol at 40° C. and hydrolysed by adding a solution of 2.8 g of sodium hydroxide in 7 cc of water. After standing at room temperature (about 25° C.) during 24 hours, the mixture was cooled to 0° C. and the separated sodium salt, filtered on a Büchner funnel and washed with ethanol. An aqueous concentrated solution of the sodium salt, was acidified with dilute hydrochloric acid and the precipitate filtered washed thoroughly with water and dried. The product—about 2.1 g of white crystals melting at 161—162° C.—was recognised as 5-benzyloxy-indole-3-β-propionic acid by a mixed melting point with an authentic sample).

The above isoamyl alcohol solution containing the main fraction of isoamyl ester was refluxed with 70 cc of hydrazide hydrate for one hour. After cooling, the solution containing the 5-benzyloxy-indole-3-β-propion-hydrazide was transferred to a separating funnel and repeatedly washed with water and, finally, with water containing a little hydrochloric acid to eliminate the excess of hydrazine. (A 35 cc sample of the dried isoamyl-alcohol solution after evaporation in vacuo gave a crystalline residue which, after crystallisation from dilute ethanol, melts at 135—136° C. and gives no depression when mixed with an authentic sample of 5-benzyloxy-indole-3-β-propion-hydrazide.)

To the above isoamyl alcohol solution of the hydrazide a solution of 12.5 g of sodium nitrite in 120 cc of water was added. After cooling to 0° C. and stirring 15.4 cc of concentrated hydrochloric acid diluted with 35 cc of water were dropped in the mixture. After standing for five minutes the isoamyl alcohol layer was separated and the aqueous phase extracted with 250 cc of isoamyl alcohol. The combined extracts, washed firstly with a dilute aqueous sodium bicarbonate solution and then with water until neutral, were dried over anhydrous potassium carbonate.

The filtered isoamyl alcohol solution, containing the 5-benzyloxy-indole-3-β-propion-azide, was refluxed for one hour in a round-bottomed flask, employing an apparatus equipped in such a way that the isoamyl alcohol refluxing in the flask was dried by contact with phosphoric anhydride. Formation of the isoamyl urethane occurred. (A 35 cc sample of the obtained solution was evaporated to dryness under reduced pressure. A concentrated benzene solution of the residual brownish oil was poured onto 10 g of aluminium oxide. Elution with benzene and evaporation to dryness of the eluates gave the β-[3-(5-benzyloxy)-indolyl]-ethyl carbamic acid isoamyl ester as a pale yellow glass which did not crystallise.)

The above isoamyl alcohol solution containing the isoamyl urethane was treated with hydrogen under continuous stirring at five atm. pressure (room temperature: about 25° C.) in presence of 20 g of 10% palladium on carbon catalyst until no more hydrogen was adsorbed (about five hours). The filtered isoamyl alcohol solution contains β-[3-(5-hydroxy)-indolyl]-ethyl carbamic acid isoamyl ester. It was then evaporated to dryness under reduced pressure.

The residue was taken up with 500 cc of ethanol and after the addition of 85 cc of water and 85 cc of concentrated hydrochloric acid was refluxed for 30 minutes to hydrolyse the carbamic ester group. The greenish solution, after addition of 10 g of crystallised sodium acetate, was neutralised to Congo red with sodium bicarbonate and filtered from the separated sodium chloride. 25 g of picric acid were added to the filtrate and most of the alcohol was evaporated under reduced pressure. Water warmed to 65° C. was added to a volume of about 400 cc. The warm solution was filtered with charcoal: by cooling 5-hydroxy-tryptamine picrate separated off as red needles M.Pt. 185—187° with dec.: after concentration of the mother liquors under reduced pressure a further amount of the same picrate was obtained. (A mixed melting point with an authentic sample gives no depression).

What we claim is:—

1. A process for the preparation of 5-hydroxy-tryptamine in which 5-benzyloxy-indole - 2-carboxyl - 3-β-propionic acid is decarboxylated by heating to 190—230° C. in order to obtain 5-benzyloxy-indole-3-β-propionic acid; the latter is esterified with an aliphatic alcohol containing up to 5 carbon atoms; the 5-benzyloxy-indole-3-β-propionic acid alkyl ester obtained is reacted with hydrazine hydrate in order to obtain 5-benzyloxy-indole-3-β-propionhydrazide; the latter is subjected to the concomitant action of sodium nitrite and an acid in the presence of an inert solvent selected from ether, benzene and its methyl homologues and aliphatic alcohols containing 4 or 5 carbon atoms; an aliphatic alcohol containing up to 5 carbon atoms or benzyl alcohol (where such an alcohol is not already present) is added to the resulting solution of the 5-benzyloxy-indole-3-β-propionazide obtained and the mixture is heated at a temperature in the range of from 60—140° C. in order to obtain a β-[3-(5-benzyloxy)-indolyl]-ethyl carbamic acid alkyl- or benzyl- ester; the latter is then subjected to catalytic hydrogenolysis and acid hydrolysis in order to obtain 5-hydroxy-tryptamine.

2. A process as claimed in claim 1 in which the β-[3 - (5-benzyloxy) - indolyl] - ethyl carbamic acid alkyl- or benzyl-ester is subjected to catalytic hydrogenolysis in the presence of a palladium catalyst in alcoholic solution and then hydrolysed with aqueous mineral acid.

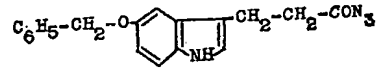
3. A process as claimed in claim 1, in which the β-[3-(5-benzyloxy)-indolyl]-ethyl carbamic acid alkyl- or benzyl-ester is hydrolysed with mineral acid, the 5-benzyloxy-tryptamine obtained is isolated in the form of its benzoate or salicylate and subjected to catalyic hydrogenolysis in the presence of a palladium catalyst.

4. A process as claimed in claim 1, in which the β-[3-(5-benzyloxy)-indolyl]-ethyl carbamic acid alkyl- or benzyl-ester is subjected simultaneously to catalytic hydrogenolysis and acid hydrolysis.

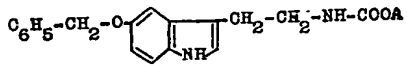
5. A process for the preparation of 5-hydroxy-tryptamine substantially as herein described with reference to the examples.

6. 5-Hydroxy-tryptamine when prepared by a process as claimed in any of the preceding claims.

7. As a new compound, 5-benzyloxy-indole-3-β-propionazide, having the formula



8. β - [3 - (5-benzyloxy) - indolyl] - ethyl carbamic acid esters having the formula



where A is a straight or branched alkyl group containing up to 5 carbon atoms or a benzyl group, when prepared by a process substantially as claimed in claim 1.

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